REMARKS

I. Status of the Claims

Pending claims 24-44 were examined and rejected. Claims 24-44 were rejected under 35 U.S.C. § 112, first paragraph, for lack of written description and/or enablement requirements. Claims 24-26 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Evans and Sommergruber. Claims 24-35 and 42 were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Denner, Cleek, and Cleek *et al.* in view of Baracchini and Friesen.

II. Statement of Priority

The Office reminded Applicants that to receive benefit of the filing date of an earlier application, the instant Application must contain a specific reference to the prior applications, as specified in 37 C.F.R. § 1.78. The Application has been amended to reference these documents.

III. Examiner's Objections

The Office objected to the specification because it did not contain an Abstract of the invention. An Abstract is enclosed on a separate sheet, as required.

In addition, the Office has not considered Reference No. 1 (DE 195 02 912 A1) listed in the IDS filed May 12, 2000, because Applicants did not provide an English translation of this German language document. Applicants have filed the English language equivalent US 6,013,639 with the accompanying IDS.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
300 I STREET, N. W.
WASHINGTON, DC 20005
202 408 4000

IV. Claim Rejections Under 35 U.S.C. § 112, first paragraph

Claims 24-44 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement and for lacking enablement. Office Action, pages 2-9.

A. Written description requirement

The Office contends that the invention comprises genera of oligonucleotides that are highly variant and the disclosure fails to provide a representative number of species to describe the genera claimed. Office Action, pages 3-4.

Applicants contend that the specification fully describes the invention under the law as set forth in *The Regents of the University of California v. Eli Lilly & Co.* 119 F.3d 1559 (Fed. Cir. 1997). In this case, the Federal Circuit held that the recitation of a nucleotide sequence of rat proinsulin cDNA was not sufficient to satisfy the written description requirement for claims directed to human, vertebrate, and mammalian cDNA. *Id.* at 1562. Rather, "an adequate written description...requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the chemical invention." *Id.* at 1566. In contrast to the *Lilly* case, the instant application provides a written description of the genus of the claimed invention through the disclosure of numerous species.

In the *Lilly* case, the Federal Circuit provided guidelines as to what level of specificity is required for nucleotide claims, such as those provided in the claimed invention. Discussing cDNA, the Court suggested that the level of specificity usually required by the written description requirement includes a recitation of the sequence of

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FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
300 I STREET, N.W.
WASHINGTON, DC 20005
202 408 4000

nucleotides that make up the cDNA. A description of a genus of cDNA may be achieved by a recitation of a representative number of cDNAs falling within the scope of the genus. It may also be accomplished by a recitation of a substantial number of structural features common to the members of the genus. *Id.* at 1569. Applicants contend that sufficient specific oligonucleotides are disclosed in the specification to provide a description of the genus.

B. Enablement

The Office also contends that the specification does not enable claims directed to compositions, kits, and methods for targeting and/or inhibiting expression of tenascin. Office Action at 4.

Applicants contend that methods for making oligonucleotides were known in the art at the time the instant application was filed, as shown by Denner, Cleek, and Baracchini. Furthermore, appropriate methods are disclosed in Example 1 of the Application, teaching the synthesis of the oligonucleotide SEQ ID NO:24. Finally, the Office has not provided any evidence that one of skill in the art would have to engage in undue experimentation to make the claimed invention.

The Office also argues that the specification fails to teach the use of the claimed oligonucleotides. However, such methods were known in the art when the Application was filed, as shown by Denner. In terms of diagnostic testing, using antisense oligonucleotides to target a particular form of tenascin, and methods of using oligonucleotides as diagnostic tools were well known in the art. For example, an

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FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
300 I STREET, N.W.
WASHINGTON, DC 20005
202 408 4000

oligonucleotide can be labeled and used as a probe to measure mRNA levels of tenascin in an individual.

The Office urges that antisense technology is so similar to gene technology that the limitations and challenges associated with gene therapy should be extended to antisense technology. Office Action at page 5. Four references were relied on to allegedly show that the field of gene therapy is unpredictable: Branch, Crooke, Palù, and BioWorld Today. Office Action at pages 5-6. All of these references were published after the priority date of November 15, 1997. According to the M.P.E.P. § 2164.05(a), the Office should not use post-filing date references to argue that a claimed invention is not enabled. Consequently, Applicants respectfully suggest that the Office's reliance on these four references is inappropriate.

If, *arguendo,* post-filing date references can be appropriately used to show enablement, there is ample evidence that both antisense technologies and gene therapy are established tools. Denner provides such an example, teaching inhibition of smooth vascular muscle cell proliferation through inhibition of tenascin expression.

The Office asserts, citing BioWorld Today, that the antisense drug 2302, developed by ISIS Pharmaceuticals, Inc. was not as promising in Phase III clinical trials as had been expected. However, another of the company's antisense drugs, ISIS 2922 (Vitravene™), has received FDA approval for treatment of cytomegalovirus retinitis. FDA website (www.fda.gov/cder/da/da0898.htm) and ISIS website (www.aegis.org/pubs/drugs/78.htm). According to the ISIS website, two additional antisense pharmaceuticals are in clinical trials and show great promise. ISIS 3521 is an antisense cancer compound that is an inhibitor of protein kinase C-alpha expression,

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FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
300 I STREET, N.W.
WASHINGTON, DC 20005
202 408 4000

which has demonstrated encouraging results. In November, 2000, the FDA granted fast track review status to the drug for non-small cell lung cancer. In Phase III clinical trials, patients with this type of cancer received ISIS 3521 in combination with carboplatin and paclitaxel. These patients survived 15.9 months, in comparison to patients who lived only 8 months on carboplatin and paclitaxel alone. ISIS website (www.isip.com/products/3521gi.htm). Patients have exhibited similar results to another antisense anti-cancer drug, ISIS 5132, which inhibits C-raf kinase. For example, in a Phase I study, one patient experienced a 97% drop in a tumor marker for ovarian cancer. Phase II trials to breast, lung, colon, pancreatic, and prostrate cancers are underway. ISIS website (www.isip.com/products/5132gi.htm). Thus, these drugs provide additional evidence that antisense therapy is rapidly developing and shows great promise.

As these references show, the comparison of antisense technology with gene therapy the technologies is inapposite, and the Office has failed to consider the differences in the technical complexity between antisense technology and gene therapy. For example, while antisense technology merely requires introducing oligonucleotides into a cell to bind mRNA, gene therapy involves a long term expression of a transgene to effect a therapeutic response. Therefore, these therapies are not analogous and the Office has not shown that antisense technology is unpredictable.

While the Office admits that the specification is enabling for the synthesis and characterization of antisense nucleotide, SEQ ID NO:24, which further comprises modified internucleotide linkages, it contends that the specification does not reasonably provide enablement for compositions or kits comprising the claimed oligonucleotides.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, DC 20005
202 408 4000

Office Action, page 4. Applicants contend that the methods required to produce appropriate compositions or kits are known by those of ordinary skill in the art.

V. Claim Rejections Under 35 U.S.C. § 102(b)

Claims 24-26 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Evans *et al.* (U.S. 5,217,867) and Sommergruber *et al.* (EU 0,564,801A1). Office Action, pages 9-10.

M.P.E.P. § 2131 recites that a "claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California,* 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The Office argues that Evans' SEQ ID NO:4 anticipates SEQ ID NO:18 of the instant invention. Therefore, the reference allegedly teaches an oligonucleotide comprising between 7-17 oligonucleotides that targets part of the tenascin gene and inhibits its expression. However, the reference does not mention tenascin. Instead, the oligonucleotide is directed against a ribosome binding site. Evans at col. 14, line 54. In addition, Evans' SEQ ID NO:4 is not identical to SEQ ID NO:18 of the instant invention.

Applicants note that SEQ ID NO:18 is written in the instant application in the 3' to 5' direction, as shown on page 5:

Correct SEQ ID NO:18 **3'**-GGTGGTACCCC-**5'**

The Examiner appears to have assumed that the sequence was written in the 5' to 3' direction:

LAW OFFICES OF
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
901 E STREET, N.W.
WASHINGTON, DC 20005
202 408 4000

Incorrect SEQ ID NO:18 **5'**-GGTGGTACCCC-**3'**

The appropriate comparison of SEQ ID NO:4 of Evans and SEQ ID NO:18 of the instant invention would be the following, and the sequences are clearly not identical:

Evans SEQ ID NO:4 5'-GTACCACCATGGGGC-3'
Instant SEQ ID NO:18 5'-CCCCATGGTGG -3'

Similarly, the Examiner alleges that Sommergruber discloses an oligonucleotide comprising 7-17 oligonucleotides that targets part of the tenascin gene and inhibits its expression. Applicants contend that the reference does not disclose an oligonucleotide directed against tenascin. Furthermore, Sommergruber's SEQ ID NO:14 is not identical to SEQ ID NO:18 of the instant invention, which as noted above is written in the 3' to 5' direction. The correct comparison of the sequences, when both are written in the same direction, is the following:

Sommergruber SEQ ID NO:14 5'-ACCACCATGGGG-3'
Instant SEQ ID NO:18 5'-CCCCATGGTGG -3'

Because the sequences disclosed in Evans and Sommergruber are not identical to those disclosed in the instant specification, they would not target the tenascin gene. Because the references do not teach each and every element of the instant invention, Applicants contend that the invention is not anticipated. Applicants respectfully request that this §102(b) rejection be withdrawn.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
300 I STREET, N.W.
WASHINGTON, DC 20005
202 408 4000

VI. Claim Rejections Under 35 U.S.C. § 103

Claims 24-35 and 42 were rejected under 35 U.S.C. § 103 as being unpatentable over Denner, Cleek, and Cleek *et al.* in view of Baracchini and Friesen. Office Action, pages 10-13.

Denner, Cleek, and Cleek *et al.* allegedly disclose antisense oligonucleotides that target and inhibit expression of the tenascin gene. The Office admits that none of these references teach oligonucleotides between 7-17 nucleotides in length. Office Action, page 11-12. Cleek *et al.* describes a oligonucleotide that is 24 nucleotides in length, having no overlap with the oligonucleotides of the instant invention. Cleek *et al.*, page 3, lines 18-19. Cleek does not list the length of the oligonucleotide in his dissertation abstract. The Office also admits that these references do not teach all of the nucleotide base and sugar modifications as set forth in the claims, including 3'-3' or 5'-5' inversions. Office Action, page 12. None of these references refer to treating vitiligo, which is an embodiment of the invention.

The Office contends that the omitted features are taught by Baracchini and Friesen. Office Action, page 12. Baracchini teaches oligonucleotides directed toward the multidrug resistance protein (MRP) that can be fewer than 17 nucleotides in length. See, for example, Baracchini, claim 26. The reference also discloses many of the modifications suggested in the claimed invention, including modified nucleotide bridges, replacements in the sugar backbone, incorporation of non-natural nucleosides, chimeric oligonucleotides, and conjugation to molecules with specific functions (e.g. to facilitate entry into the cell). Baracchini, col. 6-7. Friesen discloses oligonucleotides that can incorporate 3'-3' or 5'-5' modifications, directed toward the p24 core antigen protein of

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
901 E STREET, N.W.
WASHINGTON, DC 20005
202 408 4000

the human immunodeficiency virus. Friesen col. 1 and 3. Neither Baracchini nor Friesen discuss tenascin.

M.P.E.P. § 2142 states that to "establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine references teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Because Baracchini and Friesen do not pertain to tenascin, Applicants contend that there is no suggestion or motivation to combine the references, which is the first requirement for showing a *prima facie* case of obviousness. The mere fact that the references can be combined does not render a claimed invention obvious unless the art also suggests the desirability of the combination. While the Office has suggested that it is feasible to combine Denner, Cleek, and Cleek *et al.* with Baracchini and Friesen, it has not provided any evidence that it there was any motivation in the references themselves to do so or that it would have been desirable for one of ordinary skill in the art to combine the references.

Applicants also contend that there was no reasonable expectation of success for using oligonucleotides having fewer than 17 nucleotides in length. In fact, Denner teaches away from oligonucleotides less than 17 nucleotides in length, saying that they must be at least 18 contiguous nucleotides in length. Denner, page 3, lines 18-19.

Finally, Applicants argue that the claims are not *prima facie* obvious over the

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
300 I STREET, N.W.
WASHINGTON, DC 20005
202 408 4000

combined teachings of the cited references because they do not teach or suggest all of the limitations of the rejected claims. For example, not all of the specific sequences disclosed in claims 26, 32, 33 are taught in the references.

Applicants submit that the Office has not made a *prima facie* case that claims 24-35 and 42 are obvious over the prior art and the Examiner is requested to withdraw this rejection.

VII. Conclusion

In view of the foregoing remarks, Applicants submit that the claimed invention is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of pending claims 24-44.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: _____
Carol P. Einaudi
Reg. No. 32,220

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
300 I STREET, N. W.
WASHINGTON, DC 20005
202 408 4000